REMARKS

Applicant's counsel thanks the Examiner for the careful consideration given the application.

The claims have been amended to more clearly define the invention and to conform to US practice requirements. No new matter has been added.

SEQUENCE RULE COMPLIANCE

Each sequence disclosed in the Application has been substituted with the corresponding Sequence Identifier to comply with the sequence rules.

CLAIM REJECTIONS - 35 USC § 112

The claims and description have been amended to properly comply with the Examiner's request to fulfill current US practice.

CLAIM REJECTIONS - 35 USC § 102

Claim 1 has been amended limiting the matter to a PNA complementary to antisense strand of human *N-myc* gene. The amendment basis can be found throughout the Application, e.g. at page 7, lines 3-5. Amended Claim 1 is novel compared to the prior art, as DI *(Sun et al. Peptides,2002)* discloses a PNA complementary to sense strand of human *N-myc* gene, while the present invention, according to new Claim 1, refers to a PNA complementary to antisense strand of human *N-myc* gene. As the independent claim is novel, all the dependent claims are novel too.

CLAIM REJECTIONS - 35 USC § 103

Regarding the obviousness of the present invention, the following arguments are made.

1. It is correct that the prior art suggests *N-myc* inhibition as useful to arrest tumor growth expressing the above referred gene *(indeed the prior art shows tumor growth inhibition using antisense PNA directed against N-myc gene).*

2. Moreover it is known that the peptide PKKKRKV improves cellular up-take of PNAs. However, the Applicant invites the examiner to assess the following remarkable differences of the present invention over the prior art:

Assessment over *Sun et al.:*
Peptide nucleic acids (PNAs) comprise analogs of nucleic acids with neutral charge containing a pseudopeptide chain (backbone) instead of a common deoxyribose-phosphate structure. Peptide nucleic acids (PNAs) are enzymatically more stable if compared with oligonucleotide antisense structures.

In the present invention, peptide nucleic acid molecules, complementary to the antisense strand of human *N-myc* gene and referred to as sense PNA, are generated. *Sun et al.* use peptide nucleic acid molecules complementary to the human *N-myc* mRNA.

Regarding the above mentioned statement, the examiner should appreciate the following differences:

1. The two kinds of molecules (antisense PNA and sense anti-gene PNA) are chemically distinctive.

2. Moreover, the two molecules (antisense PNA and sense anti-gene PNA) affect two different targets: RNA and DNA, respectively.

3. The mechanisms of action by which these molecules function are completely distinguishable.

Looking at these relevant differences, the Applicant considers not so obvious the improved down-regulation of *N-myc* expression obtained in the present invention using sense anti-gene PNA with respect to the use of the antisense PNA cited in the prior art. As a demonstration, please refer to the comparative example of Fig. 2 of the Application as filed, wherein the inhibition effect of treatment with sense anti-gene PNA and antisense anti-gene PNA on the proliferation of GI-LI-N and IMR-32 cells (with amplified N-myc gene expression) after 48 hours has been reported. The examiner can appreciate that antisense anti-gene PNA do not show any inhibition effect compared to sense anti-gene PNA molecules.

Assessment over *Cutrona et al.:*

The Applicant acknowledges that, looking at *Cutrona et al.,* the skilled person learns that the peptide PKKKRKV improves cellular up-take of PNAs. However, the Applicant invites the Examiner to focus his attention on the molecular systems where the PNA/PKKKRKV-conjugated have been used.

In details:

Cutrona et al. work with a cellular model of Burkitt lymphoma.

This cell line is characterized by *c-myc* overexpression caused by its translocation from chromosome 8 to chromosome 14, often close to the enhancer of the immunoglobulin heavy chain locus (IgH).

The neuroblastoma cell line, used in the present invention, instead, is characterized by *N-myc* overexpression caused by N-myc DNA amplification from 3 to 1500 copies.

The Applicant desires to stress the following differences between the two above disclosed cellular models:

1) The two *myc* genes used in the models are not IDENTICAL, but they are RELATED genes belonging to the same family. The referring genes are *c-myc* and *N-myc*.

2) The up-regulation of *myc* gene in the two above disclosed cell lines is caused by two completely different mechanisms. In particular, in the cellular model of the present invention the gene copy number is increased, compared to the cellular model used by *Cutrona et al.,* where *myc* upregulation is a consequence of a translocation under IgH enhancer.

Looking at the observations above reported, the Applicant believes that *myc* gene downregulation, by administering the sense anti-gene PNA of the invention in the cell line of the present Application and in the cell line used by *Cutrona et al.,* would provide results significantly different between the two cellular models, and therefore unpredictable for a skilled person.

As a result, the disclosure of *Cutrona et al.* does not suggest the present invention as

claimed.

In view of the present amendments and argumentation, it is clear that this application is now in condition for allowance, which is respectfully requested. If any further fees are required by this communication, please charge such fees to our Deposit Account No. 16-0820, Order No. BUG5-38919.

Respectfully submitted,
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